REMARKS

Claims 1-39 are pending and claims 19-31 are under consideration in this application, claims 1-18 and 32-39 having been withdrawn for allegedly being drawn to separate inventions.

No new matter is added by any of the amendments made herein.

Applicants respectfully request that the amendments made herein be entered. These amendments were made largely to enhance the clarity of relevant claims, to incorporate embodiments of dependent claims into appropriate independent claims, to cancel the relevant dependent claims, and to correct the dependency of other dependent claims. If the amendments are entered, claims 1- 19, 21-26, and 28-39 will be pending and claims 19, 21-26, and 28-31 will be under consideration in this application, claims 20 and 27 having been cancelled herein.

35 U.S.C. § 112, second paragraph, rejections

Claims 19-31 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse the rejection.

(A) From the comments on page 3, lines 9-18, of the Office Action, Applicants understand the Examiner's position to be that, while one of ordinary skill in the art would be reasonably apprised of what constitutes identifying subjects suspected of having, or likely to develop, graft rejection responses, the term "identifying" with respect to the other conditions falling within the scope of claims 19-31 is vague and indefinite. Applicants respectfully disagree with this position.

First, the Office Action does provides neither a rebuttal of the arguments provided in the Amendment and Response filed November 10, 2006, in regard to this issue, nor a basis for the assertion that term "identifying" with respect to conditions other than graft rejection is vague and indefinite. Applicants believe, for the reasons recited on page 16 of the prior Amendment and Response, that the term is not indefinite with respect to subjects that are either suspected of having or are likely to develop the relevant conditions. However, in order to expedite

prosecution of the present application, Applicants have deleted the term "likely to develop" from the claims.

In regard to the term "suspected of having," Applicants respectfully submit that one skilled in the art would believe that a relevant subject would be one having at least one symptom of an appropriate condition; such an artisan would unlikely consider a subject having no symptoms of the condition to be "suspected of having" the condition. As pointed out on page 16, paragraph 3, of the prior response, symptoms of many conditions, including autoimmune diseases (as now specified by the claims), are well-known to those skilled in the art (e.g., medical professionals). Moreover, where one (or more) symptoms of a particular autoimmune disease are also observed in a wide variety of other conditions, such artisans would know that, in order to classify a subject as one "suspected of having a particular autoimmune disease", they would need to examine the subject for the presence of more symptoms than if the autoimmune disease was characterized by one or more autoimmune disease-specific symptoms. Applicants acknowledge that the type and number of symptoms required for a test subject to be designated as "suspected of having" a condition will vary greatly from condition to condition. However, Applicants respectfully submit that this variability by no means equates with vagueness or indefiniteness and that, in light of these considerations, those skilled in the art would likely not differ greatly in the range of subjects that they would consider to be those "suspected of having" an appropriate autoimmune disease.

(B) From the comments on page 3, line 19, to page 4, line 10, of the Office Action, Applicants understand the Examiner's position to be that in claims 19-24 the term "elevated" is indefinite because: (1) one ordinarily skilled in the art would not be apprised as to which of a plurality of "normal levels" to use; and (2) the specification does not provide a definition of the term or a standard for ascertaining the requisite degree of elevation. Applicants respectfully disagree with this position.

Applicants submit that the invention is not limited by methods of establishing "normal" values and that any of a number of possible "normal" values can be used in the methods specified by the instant claims. One skilled in the art would know, for example, that if there is a relatively low level of variability between subjects not suspected of having an autoimmune disease of

interest, a "normal" value could be the mean value of a relatively low number of such subjects, a mean of values obtained from the general population, or even a value obtained, prior to the onset of symptoms, from a particular subject suspected of having the autoimmune disease. On the other hand, if there is a relatively high level of variability between subjects not suspected of having the autoimmune disease, such an artisan would know that a "normal" value would need to be the average of a relatively large number of subjects, the subjects in an extreme case being only those established not to have the condition of interest. Moreover, in certain cases, it is even possible that, for example, the level of anti-B7-H1 antibodies in subjects with an autoimmune disease of interest would not be statistically different from any of the above-recited possible "normal" levels. In such cases it would of course not be possible to perform the method of the instant claims. In this regard, Applicants point out that it is not required for patentability that each and every species of a claimed genus function as claimed. The Examiner's attention is drawn to the following quotation from the USPTO's Manual of Patent Examining Procedure (MPEP):

> The presence of inoperative embodiments within the scope of the claims does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. MPEP § 2164.08(b), citing *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)

Establishing appropriate control subjects, the number of control subjects, and the feasibility of applying the method of the instant claims are all routinely performed by, for example, clinical scientists, frequently in consultation with statisticians. As pointed out above for ascertaining subjects that are "suspected of having" a condition of interest, Applicants respectfully submit that variability in establishing "normal" values for the methods of the instant claims does not equate in any way with vagueness or indefiniteness. For any disease or condition and/or assay for anti-B7-H1 antibodies, one skilled in the art would know exactly how to proceed to establish an appropriate "normal" level of anti-B7-H1 antibodies and hence determine what constitutes an "elevated" level.

(C) From the comments on page 4, line 11, to page 5, line 6, of the Office Action, Applicants understand the Examiner's position to be that claims 25-31 are indefinite because the specification does not provide guidance on what methods are used to establish "standard" levels of disease progression. Applicants respectfully disagree with this position.

Applicants point out that the invention embodied by the claims at issue is not directed to, or limited by, any particular methods of determining the relevant "standard" levels. The invention is based on the finding that the presence of certain diseases that are mediated directly or indirectly by activated T cells, and in particular the active phases of those diseases, correlates with the presence of elevated levels of anti-B7-H1 antibodies in relevant subjects. In a manner essentially the same as that described above for establishing "normal" levels for a particular condition and/or assay, subjects and methods used for establishing such "standard" values would likely differ significantly from one autoimmune disease to another, depending on, for example, the variability in the levels of anti-B7-H1 antibodies in subjects established to have particular stages of relevant autoimmune diseases. Again this variability in methodology does not equate at all with either vagueness or indefiniteness. As in establishing the "normal" levels, for any one condition and/or assay, one skilled in the art would know exactly how to proceed in order to establish the relevant "standard" levels for use in the methods embodied by the claims at issue.

In light of the above considerations and amendments, Applicants request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

35 U.S.C. § 112, first paragraph, rejections

(a) Claims 19-31 stand rejected as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

From the comments on page 5, line 7, to page 6, line 12, of the Office Action, Applicants understand the Examiner's position to be that the term "human B7-H1" lacks "written description" by the specification because the skilled artisan could not envision all the contemplated amino acid sequence possibilities encompassed by the claims at issue. Applicants respectfully disagree with this position.

First, with respect to the comments on page 6, lines 1-9, of the Office Action, Applicants point out that the text cited by the Examiner actually states that "polypeptides useful in the invention include variant polypeptides include variant polypeptides" rather than "polypeptides of the instant invention include variant polypeptides." Nevertheless, even in the latter case, Applicants respectfully submit that one skilled in the art would not construe the text to be a definition of "B7-H1 polypeptides" but rather to be a recitation of what types of polypeptides are included in the invention and to provide written description for the explicit recitation of variant polypeptides in relevant claims of interest. Notwithstanding these considerations, in order to expedite prosecution of the instant application, claims 19 and 25 have been amended to specify that the antibodies used in the claimed methods bind to "human wild-type B7-H1." These amendments are supported by the specification (e.g., the paragraph spanning pages 3 and 4) and render the rejection moot.

(b) Claims 19-20, 24-27, and 31 stand rejected as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention.

From the comments on page 6, line 13, to page 7, line 6, of the Office Action, Applicants understand the Examiner's position to be that the specification does not provide a sufficient enabling description of the claimed method of diagnosing, and the claimed method of monitoring the progress of, a disease with symptoms caused by activation of T cells or an autoimmune disease.

Applicants submit that, in view of: (a) the diversity in the etiology, target organs, and symptoms of the conditions for which the Examiner finds there to be sufficient enablement (rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and autoimmune hearing loss (AHL)) in the claimed methods, and (b) the well-established direct or indirect role of T cells in all three, one skilled in the art would believe it extremely likely that elevated levels of anti-B7-H1 antibodies would occur in subjects having any of a very wide range of diseases or conditions whose symptoms are caused, directly or indirectly, by activated T cells. Nevertheless, in order to expedite prosecution of the instant application, Applicants have amended independent claims 19 and 25 to specify autoimmune diseases (see above), cancelled claims 20 and 27 specifying

autoimmune diseases, and amended claims 21-23 and 28-30 to change their dependency from cancelled claims 20 and 27, respectively, to independent claims 19 and 25, respectively.

Again, Applicants emphasize the diversity in the etiology, target organs, and symptoms of the three autoimmune diseases for which the Examiner believes there is sufficient enablement for the claimed methods. Thus, the symptoms of RA are generally believed to be due largely to cellular immune responses (see, for example, MacKenzie (2006) Drug Discovery Today 11(19): 952-956, paragraph spanning pages 952 and 953; copy enclosed as Exhibit A) while those of SLE are considered to be due to humoral (antibody) immune responses (see, for example, Silverman (2006) Bulletin of the NYU Hospital for Joint Diseases 64(1 and 2):51-56, page 51, column 1, second paragraph, lines 6-7; copy enclosed as Exhibit B). While AHL has not been studied in as much detail as RA and SLE, it seems that its symptoms may be due to cellular and humoral immune responses (see, for example, Solares et al. (2003) J. Neuroimmunol. 138:1-7; copy enclosed as Exhibit C). Nevertheless, as in all autoimmune diseases, whether they are mediated by cellular or antibody immune responses, activated T cells are likely, directly or indirectly, involved in the etiology of all three diseases. Thus, where the symptoms of an autoimmune disease are caused by a cellular immune response, soluble factors (e.g., cytokines) released by activated T cells cause the relevant tissue damage-related symptoms. Moreover, in an autoimmune disease where the symptoms are due to an antibody response, while the relevant antibodies are produced by activated B cells, the responses of such B cells usually require the helper activity of activated T cells.

With respect to target organs or tissues and symptoms, in RA there is inflammation and swelling of the synovial membrane and neighboring structures in joints (see, for example, MacKenzie, *supra*, page 952, column 1, second paragraph, lines 1-3). In SLE there is generally involvement of any or all of a wide range of tissues and organs, including heart, lungs, kidneys, the nervous system, the gastrointestinal system, and bone marrow (see, for example, Klippel (1997) J. Rheumatol. 24(suppl. 48):67-71, Table 1 on page 67; copy enclosed as Exhibit D). AHL is an inflammatory condition of the inner ear that results in hearing loss and, in some cases, vertigo (see, for example, Bovo et al. (2006) Acta Oto-Laryngologica 126: 1012-1021, Abstract; copy enclosed as Exhibit E).

In light of the above considerations, Applicants submit that one skilled in the art would know that, even though autoimmune diseases may differ substantially in their "downstream" etiology, target organs, and symptoms, activated T cells play an important role in at least the substantial majority. Moreover, in view of this knowledge and the findings (reported for in the instant specification) that elevated levels of anti-B7-H1 antibodies are detectable in three autoimmune diseases that cover the spectrum of autoimmune diseases in terms etiology (i.e., cellular versus humoral immune responses) and in which a diverse range of target organs and symptoms are involved, such an artisan would believe that elevated levels of anti-B7-H1 antibodies would be detectable in subjects having a wide variety of, if not all, autoimmune diseases. Moreover, being in possession of the teachings of the working examples in the instant specification and his own knowledge and expertise, he or she would be able to determine by simple and routine experimentation whether in subjects having any particular autoimmune disease of interest there are indeed elevated levels of anti-B7-H1 antibodies. In this regard, Applicants again point out that it is not required for patentability that each and every species of a claimed genus function as claimed.

With respect to the text on page 6, line 23, to page 7, line 1, of the Office Action, Applicants point out that, as recited on page 22, lines 6-11, of the prior Amendment and Response, the instant specification, and not only Dong et al. (J. Clin. Investig. (2003) 111:363-370), teaches that elevations in the levels of B7-H1-specific antibodies similar to those described in detail for in the examples for RA were also seen in SLE and AHL patients.

In view of the above considerations and amendments, Applicants respectfully submit that one skilled in the art would be able, without undue experimentation, to practice the invention as embodied by the instant claims. Therefore Applicants respectfully request that the rejection for lack of enablement be withdrawn.

CONCLUSION

In summary, in view of the amendments and remarks set forth above, Applicants maintain that all of the pending claims patentably define the invention. Applicants request that the Examiner permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number below.

Enclosed is a request for an automatic extension of time. Please apply the charge for the extension of time and any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07039-443001.

Respectfully submitted,

Date: 5/3/07

Stuart Macphail, Ph.D., J.D.
Reg. No. 44,217

Fish & Richardson P.C.
Citigroup Center
52nd Floor
153 East 53rd Street
New York, New York 10022-4611
Telephone: (212) 765-5070
Facsimile: (212) 258-2291